ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitor and insulin combination treatment in type 2 diabetes and chronic kidney disease: A meta-analysis

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ABSTRACT

Aims/Introduction: The union of dipeptidyl peptidase-4 inhibitors and insulin in patients with type 2 diabetes and chronic kidney disease provides satisfactory glucose management without increasing adverse events (AEs). This research appraised the therapeutic effect and safety of combination therapy in patients with type 2 diabetes and chronic kidney disease.

Materials and Methods: We carried out a meta-analysis of randomized controlled trials to analyze AEs, hypoglycemia, serious AEs, severe hypoglycemia, estimated glomerular filtration rate, fasting plasma glucose, glycated hemoglobin, insulin dose, low-density lipoprotein cholesterol, uric acid and weight between combination treatment groups and control groups by searching the Cochrane Library, Excerpta Medica Database (Embase), PubMed and Web of Science databanks until October 2020.

Results: Five studies (6 trials, 1,278 participants) met the inclusion criteria. The evidence quality ranged from moderate to high. Glycated hemoglobin (standardized mean difference −0.29, 95% confidence interval −0.44 to −0.14) and insulin dose (standardized mean difference −0.16, 95% confidence interval −0.29 to −0.02) were obviously smaller in the combination cure patients than in the control patients. Compared with the control groups, combination treatment did not increase AEs, hypoglycemia, serious AEs or severe hypoglycemia.

Conclusions: This study showed the effectiveness and safety of dipeptidyl peptidase-4 inhibitors bonded with insulin in patients with type 2 diabetes and chronic kidney disease, but the protective actions of this cure on kidney and cardiovascular outcomes, as well as the functions of other dipeptidyl peptidase-4 inhibitors, need to be affirmed by more good-quality randomized controlled trials.

INTRODUCTION

There were probably 451 million persons with diabetes mellitus around the world in 2017, and the figure is projected to go up to 693 million in 2045[1]. Chronic kidney disease (CKD) is present in approximately 40% of patients with type 2 diabetes[2]. Type 2 diabetes, as the main cause of CKD, promotes the progression of CKD[3–6]. Patients with type 2 diabetes and CKD have a lower quality of life and worse prognosis[7–10]. Due to the reduction in drug clearance and the decrease in renal

gluconeogenesis, these patients are more prone to adverse events (AEs), such as hypoglycemia, and have a lower glycemic compliance rate[11–14]. Insulin therapy is common in patients with CKD, and major antidiabetic medicines need to be adjusted[15]. As this kind of patient is very common and difficult to treat, there is an urgent need for a new safe and effective treatment.

Because dipeptidyl peptidase-4 (DPP-4) inhibitors depend on glucose intake, the danger of hypoglycemia is low, and they can be used in patients with type 2 diabetes and CKD[16]. A study has shown that DPP-4 inhibitors combined with insulin

can better reduce glycated hemoglobin (HbA1C) and insulin doses without increasing hypoglycemic events[17]. Some studies suggest that single or combined usage of DPP-4 inhibitors in patients with type 2 diabetes and CKD can ameliorate glycemic control without increasing AEs[18–21]. DPP-4 inhibitors also have renal protective effects and do not affect weight[22–24].

The aim of this work was to conclude whether the combination of DPP-4 inhibitors and insulin could ameliorate blood glucose management in patients with type 2 diabetes and CKD without augmenting AEs through a meta-analysis of randomized controlled trials (RCTs).

MATERIALS AND METHODS

The present meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[25] and was signed up for the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020211355).

Literature search strategy

We searched studies on DPP-4 inhibitors, insulin, type 2 diabetes, chronic kidney disease and RCTs in the Cochrane Library, Excerpta Medica Database (Embase), PubMed and Web of Science databanks in October 2020. The follow-up Medical Subject Headings (MeSH) terms served for retrieval were: "Linagliptin", "Sitagliptin Phosphate", "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination", "Vildagliptin", "Dipeptidyl-Peptidase IV Inhibitors", "Insulin", "Insulin, Regular, Human", "Isophane Insulin, Human", "Insulin, Regular, Pork", "C-Peptide", "Proinsulin", "Insulin, Short-Acting", "Insulin Aspart", "Insulin Lispro", "Insulin, Long-Acting", "Insulin Detemir", "Insulin Glargine", "Insulin, Isophane", "Insulin, Lente", "Insulin, Ultralente", "Biphasic Insulins", "Insulins", "Diabetes Mellitus, Type 2", "Diabetes Mellitus, Lipoatrophic", "Renal Insufficiency, Chronic", "Kidney Failure, Chronic", "Frasier Syndrome" and "Chronic Kidney Disease-Mineral and Bone Disorder". References for the studies were searched, and the date of publication and language of the studies were unlimited.

According to Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, CKD is defined as an abnormality of kidney structure or function that exists for >3 months and has health implications[26]. Study patients met the following inclusion criteria: (i) had type 2 diabetes and CKD; and (ii) any sex or age. Patients in the intervention groups were remedied with the following: (i) a union of DPP-4 inhibitor and insulin; or (ii) DPP-4 inhibitor and insulin plus background therapies (e.g., drugs and/or hemodialysis), and the background therapies were also used in the control groups. The treatment of patients in the control groups involved the following: (i) placebo or no treatment; (ii) placebo or no treatment plus background therapies (e.g., drugs and/or hemodialysis); (iii) DPP-4 inhibitor or insulin monotherapy; or (iv) DPP-4 inhibitor or insulin plus background therapies (e.g., drugs and/or

hemodialysis), which were also used in the intervention groups. The type of study was limited to RCTs. The languages of the studies were unlimited. The results of the studies included the following: (i) incidence of AEs, hypoglycemia, serious adverse events (sAEs) and severe hypoglycemia; and (ii) mean change from baseline to end-point of estimated glomerular filtration rate (eGFR), fasting plasma glucose (FPG), HbA1C, insulin dose, low-density lipoprotein cholesterol (LDL-C), uric acid (UA) and weight.

The exclusion criteria were (a) crossover trials and (b) trials without available results.

Data extraction procedure

Two researchers independently extracted data kept to the inclusion and exclusion norms. The disputes were settled by a third researcher. The subsequent details were abstracted from the literature that fulfilled the norms: author, year, country, age, sex, diabetes duration, sample size, treatment duration, microalbuminuria, eGFR, CKD stage, treatment and outcomes (AEs, sAEs, eGFR, FPG, HbA1C, LDL-C, UA, hypoglycemia, severe hypoglycemia, insulin dose, weight). In the results, the dichotomous variables were expressed as percentages, and the continuous variables were represented as the mean ± standard deviation (SD). The title, abstract, full text and references of each included study were carefully reviewed to avoid omitting appropriate studies.

Grading of evidence

We used RevMan 5.4 (The Cochrane Collaboration, London, UK)[27] of the Cochrane Collaboration to evaluate the risk of bias in RCTs and GRADEprofiler 3.6.1 (The GRADE Working Group; Rome, Italy) of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group to value the quality of evidence in RCTs.

Statistical analysis

We included RCTs that contrasted the effectiveness and safety of DPP-4 inhibitors and insulin combination cure with other treatments (placebo, no treatment, DPP-4 inhibitors or insulin alone) in patients with type 2 diabetes and CKD. We extracted 11 outcomes: (i) main outcomes: AEs, HbA1C, hypoglycemia, insulin dose, sAEs and severe hypoglycemia; and (ii) secondary outcomes: eGFR, FPG, LDL-C, UA and weight. With these results, we comprehensively valued the impacts of DPP-4 inhibitor and insulin combination therapy on patients with type 2 diabetes and CKD.

The ratio of the incidence of AEs, hypoglycemia, sAEs and severe hypoglycemia between the intervention patients and the control patients during treatment was taken as the relative risk (RR). The difference in the average changes in HbA1C, insulin dose, eGFR, FPG, LDL-C, UA and weight between the intervention patients and the control patients before and after treatment was taken as the standardized mean difference (SMD). Some studies did not provide SD directly, and the standard

error, median and quartile were converted to SD[28]. The incidences of AEs, hypoglycemia, sAEs and severe hypoglycemia were dichotomous variables, and the effect size (ES) was RR, whereas the changes in HbA1C, insulin dose, eGFR, FPG, LDL-C, UA and weight were continuous variables, and the ES was SMD. The Cochran Q test and *I*-squared (I^2) test were utilized to test heterogeneity between studies, and $P < 0.1$ showed heterogeneity, whereas $I^2 \geq 50\%$ showed moderate and severe heterogeneity[29,30]. Regardless of the heterogeneity, the random effects model served to combine the ES[31]. We carried out subgroup analyses according to the drugs and CKD stages, detected the source of heterogeneity by the Galbraith method, and analyzed the effect of a single study on the total effect. As a result of the small number of studies, there was no publication bias test[32]. The forest plot achieved the consequences of the meta-analysis by showing the influences of each subgroup and the overall effect. All data were analyzed by Stata 12.0 (StataCorp LP, College Station, TX, USA). All data are expressed as the 95% confidence interval (CI) of ES. Unless otherwise stated, we used $P < 0.05$ to manifest that the difference was statistically significant.

RESULTS

Selection and characteristics of studies

We retrieved 383 studies from the databases, 19 studies from references, excluded 397 studies and finally included five studies (6 trials, 1,278 participants) for meta-analysis (Figure S1). All five studies were published between 2013 and 2020, the treatment duration ranged between 12 and 52 weeks, and the intervention drugs included linagliptin and vildagliptin (Table S1)[33–37]. Four studies reported the baseline CKD stage, and one reported baseline microalbuminuria (Table S1)[33–37]. The results of four studies included AEs, five studies included sAEs, two studies included eGFR, two studies included FPG, five studies included HbA1C, three studies included hypoglycemia, four studies included severe hypoglycemia, three studies included weight, four studies included insulin dose, two studies included LDL-C and two studies included UA (Table S1)[33–37].

Lukashevich *et al.*[33] contrasted "vildagliptin 50 mg/day + insulin" and "placebo + insulin", Munch *et al.* contrasted "vildagliptin 50 mg/day + insulin" and "insulin", Yagoglu *et al.*[37] compared "linagliptin 5 mg/day + insulin" with "insulin", and Zhu *et al.*[35] compared "linagliptin + insulin" with "placebo + insulin" (Table S1). McGill *et al.*[34] analyzed two trials: McGill-1 and McGill-2, and McGill-1 included two subgroups: McGill-1-A and McGill-1-B. McGill-1-A compared "CKD stage 2" and "linagliptin 5 mg/day + insulin" with "CKD stage 2" and "placebo + insulin", McGill-1-B compared "CKD stage 3" and "linagliptin 5 mg/day + insulin" with "CKD stage 3" and "placebo + insulin", and McGill-2 compared "CKD stages 4-5" and "linagliptin 5 mg/day + insulin" with "CKD stages 4-5" and "placebo + insulin" (Table S1). The results of all studies are shown in Table S2.

Bias of studies

A summary of bias risks for all studies is shown in Figure S2. The research of Munch *et al.*[36], Yagoglu *et al.*[37] and Zhu *et al.*[35] had performance bias and detection bias of unclear risk, whereas other studies had low bias risk.

Outcomes

AEs

We carried out subgroup analyses based on interventions and CKD stages (4 studies, 1,218 participants)[33–37]. There was no meaningful disparity in the occurrence of AEs between linagliptin or vildagliptin combined with insulin and the control group (linagliptin: RR 0.98, 95% CI 0.90–1.07, $P = 0.638$; vildagliptin: RR 1.18, 95% CI 0.81–1.73, $P = 0.388$; Figure 1). There was no distinct disparity in the occurrence of AEs between CKD stages 1 or 2 or CKD stages 3–5 patients treated with DPP-4 inhibitors and insulin contrasted with the control group (CKD stages 1 or 2: RR 0.95, 95% CI 0.88–1.03, $P = 0.234$; CKD stages 3–5: RR 1.02, 95% CI 0.93–1.13, $P = 0.661$; Figure 2). There was not great heterogeneity (overall: $I^2 = 43.9\%$, $P = 0.129$; Figures 1 and 2).

Hypoglycemia

Interventions and CKD stages were used for subgroup analyses (3 studies, 1,054 participants)[32,33,35]. Linagliptin or vildagliptin combined with insulin did not augment the occurrence of hypoglycemia contrasted with the control group (linagliptin: RR 1.04, 95% CI 0.81–1.35, $P = 0.746$; vildagliptin: RR 1.38, 95% CI 0.83–2.29, $P = 0.218$; Figure 3). Compared with the control group, linagliptin or vildagliptin combined with insulin did not raise the occurrence of hypoglycemia in patients with CKD stages 1 or 2 or CKD stages 3–5 (CKD stages 1 or 2: RR 0.93, 95% CI 0.75–1.16, $P = 0.529$; CKD stages 3–5: RR 1.22, 95% CI 0.96–1.54, $P = 0.103$; Figure 4). The heterogeneity among studies was mild (overall: $I^2 = 21.4\%$, $P = 0.278$; Figures 3 and 4).

HbA1C

We carried out subgroup analyses according to the interventions (5 studies, 1,258 participants)[33–37] and CKD stages (4 studies, 1,198 participants)[33,34,36,37]. The combination of linagliptin and insulin could obviously reduce HbA1C contrasted with the control patients, but there was not valid disparity between the combination of vildagliptin and insulin and the control patients (linagliptin: SMD −0.29, 95% CI −0.48 to −0.10, $P = 0.003$; vildagliptin: SMD −0.22, 95% CI −0.47 to 0.04, $P = 0.095$; and overall: SMD −0.29, 95% CI −0.44 to −0.14, $P = 0.000$; Figure 5). There was not distinct heterogeneity (overall: $I^2 = 33.6\%$, $P = 0.172$; Figure 5). The combination of DPP-4 inhibitors and insulin significantly reduced HbA1C in patients with CKD stages 1 or 2 and CKD stages 3 to 5 compared with the control group (CKD stages 1 or 2: SMD −0.51, 95% CI −0.67 to −0.34, $P = 0.000$; CKD stages 3–5: SMD −0.22, 95% CI −0.38 to −0.07, $P = 0.005$; and overall: SMD −
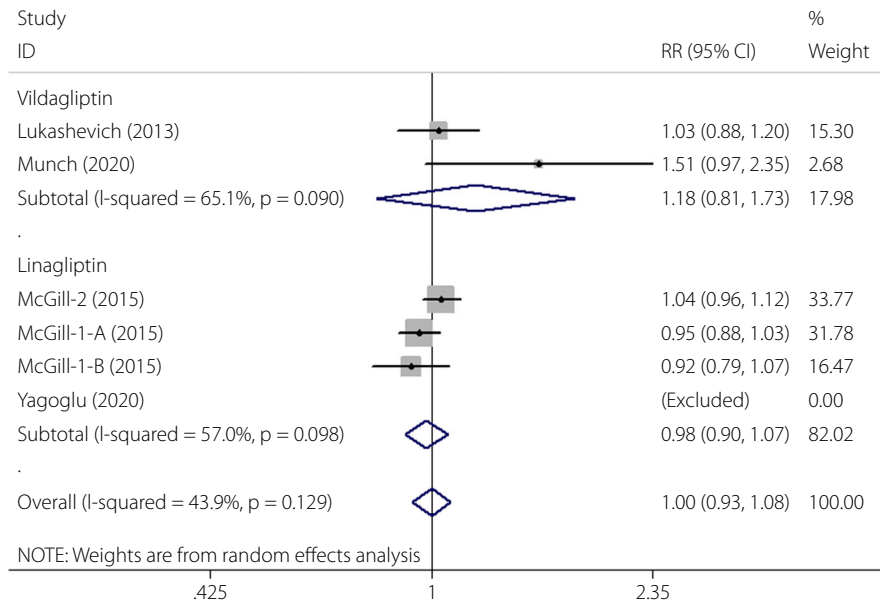
Figure 1 | Forest plot comparing adverse events of groups treated with linagliptin or vildagliptin combined with insulin versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; RR, relative risk.
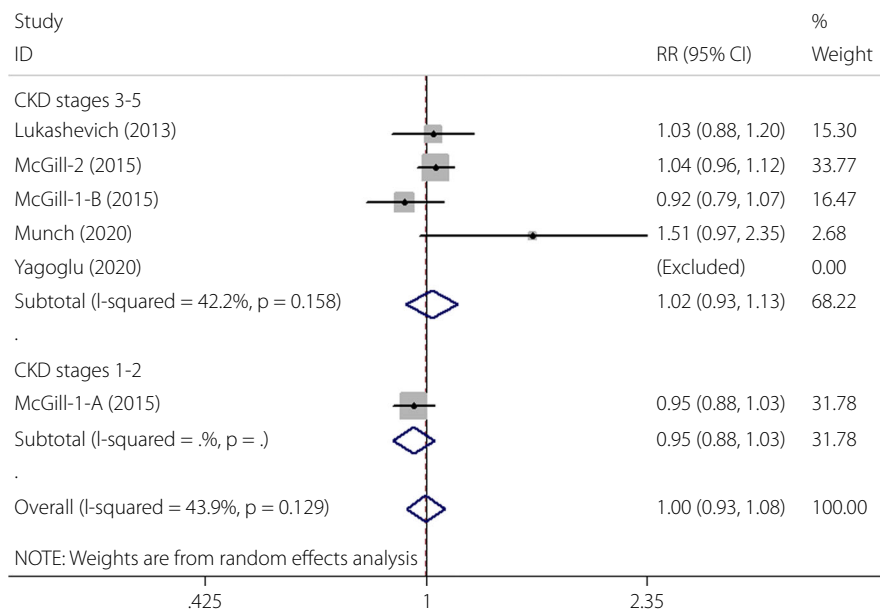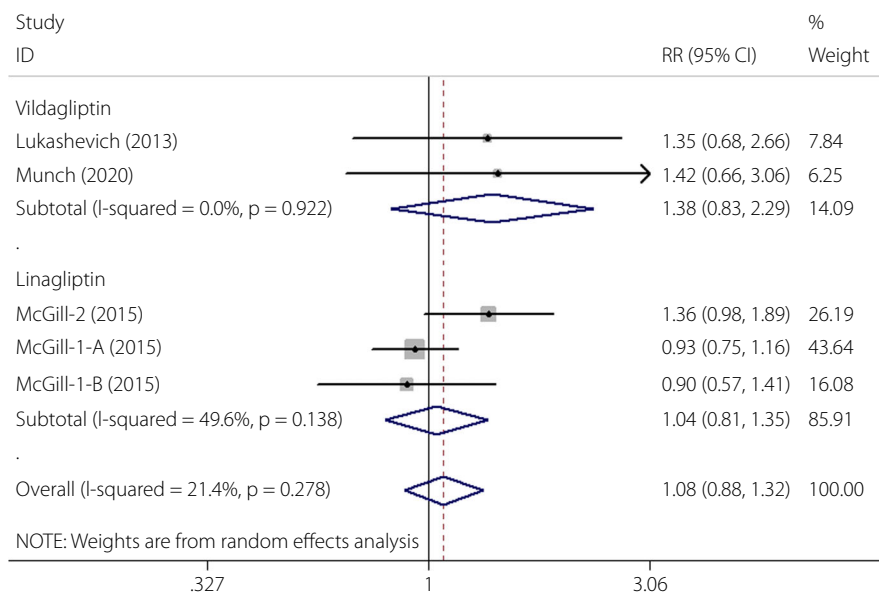

Figure 2 | Forest plot comparing adverse events of groups with chronic kidney disease (CKD) stages 1-2 or CKD stages 3–5 versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; RR, relative risk.

0.33, 95% CI −0.47 to −0.19, $P = 0.000$; Figure 6). Heterogeneity was not obvious (overall: $I^2 = 22.3\%$, $P = 0.266$; Figure 6).

sAEs
We carried out a subgroup analysis based on interventions (5 studies, 1,278 participants)[33–37]. There was no important difference in the incidence of sAEs between linagliptin or vildagliptin combined with insulin and the control group (linagliptin: RR 0.99, 95% CI 0.75–1.31, $P = 0.944$; vildagliptin: RR 0.71, 95% CI 0.43–1.16, $P = 0.172$; Figure S3). There was little heterogeneity between studies (overall: $I^2 = 0.0\%$, $P = 0.808$; Figure S3).

Figure 3 | Forest plot comparing hypoglycemia of groups treated with linagliptin or vildagliptin combined with insulin versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; RR, relative risk.
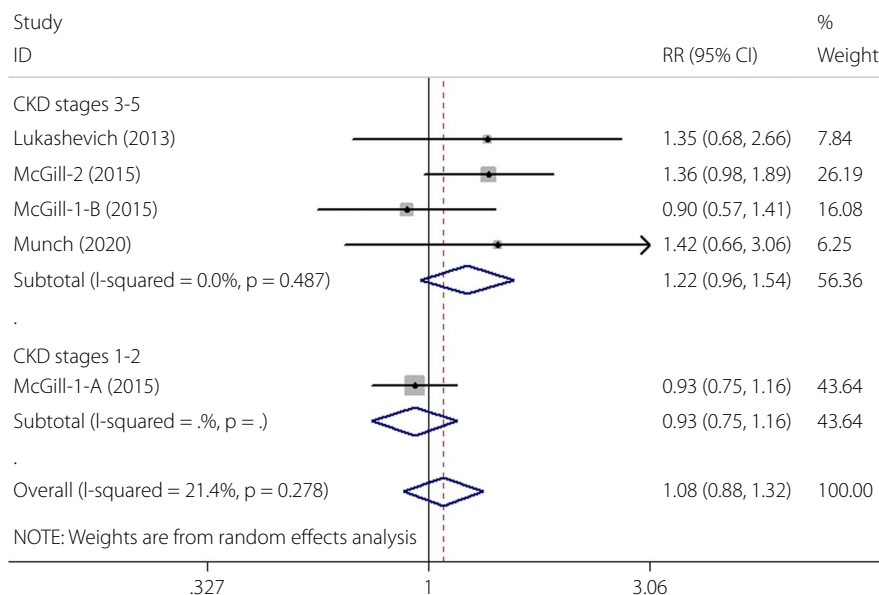
Figure 4 | Forest plot comparing hypoglycemia of groups with chronic kidney disease (CKD) stages 1-2 or CKD stages 3–5 versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; RR, relative risk.

Severe hypoglycemia

We used interventions for subgroup analysis (4 studies, 1114 participants)[33–36]. There was not an effective difference in the occurrence of severe hypoglycemia between linagliptin or vildagliptin combined with insulin and the control group (linagliptin: RR 1.38, 95% CI 0.56–3.40, $P = 0.486$; vildagliptin: RR 0.90, 95% CI 0.23–3.49, $P = 0.878$; Figure S4). The

heterogeneity between studies was very small (overall: $I^2 = 0.0\%$, $P = 0.959$; Figure S4).

Insulin dose

Interventions were used for subgroup analysis (4 studies, 1,082 participants)[34–37]. The combination of linagliptin and insulin could significantly reduce the insulin dose compared with the
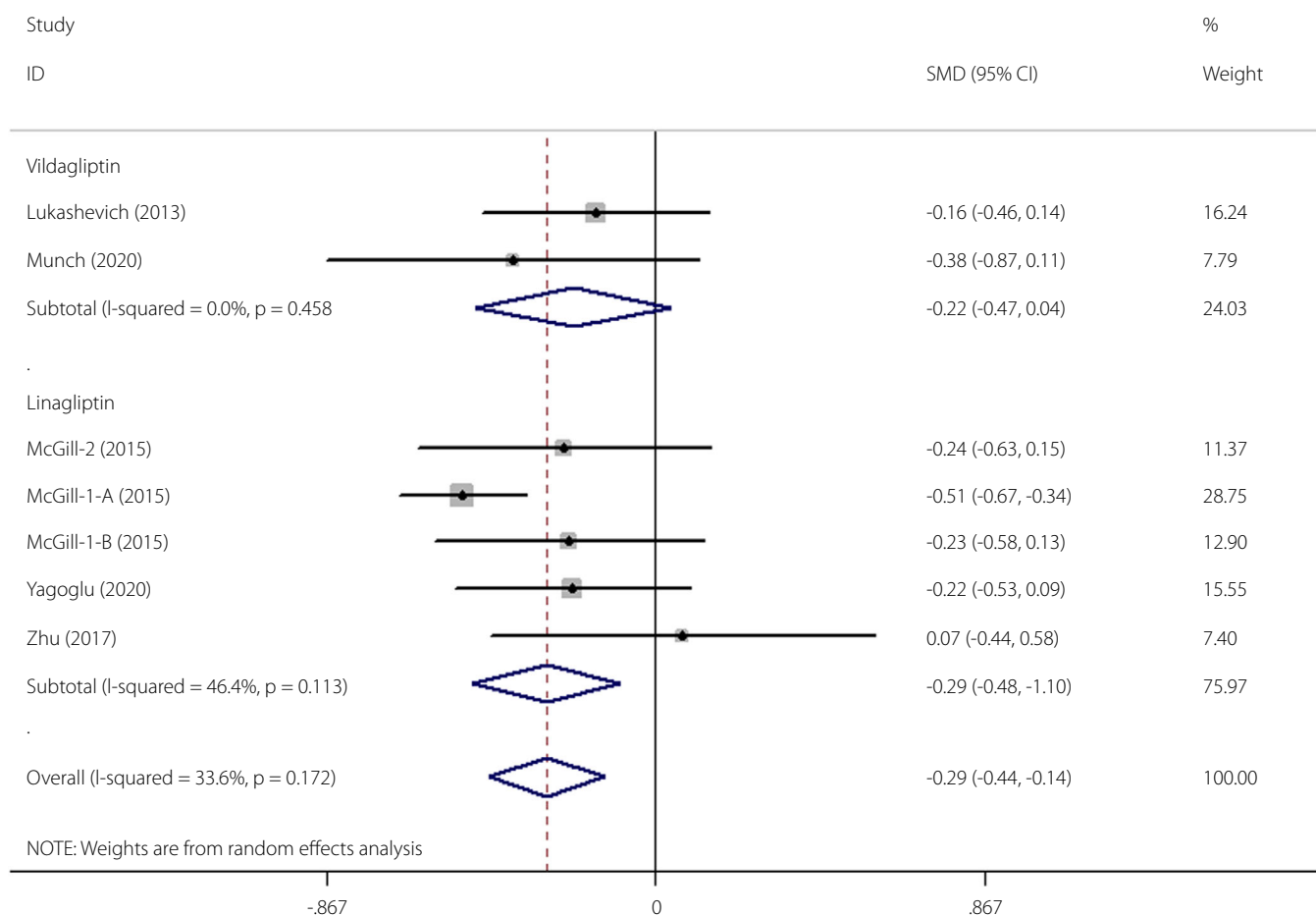
Figure 5 | Forest plot comparing glycated hemoglobin (HbA1C) of groups treated with linagliptin or vildagliptin combined with insulin versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; SMD, standardized mean difference.

control group, but there was not an important disparity between the combination of vildagliptin and insulin and the control group (linagliptin: SMD −0.17, 95% CI −0.33 to −0.01, $P = 0.035$; vildagliptin: SMD −0.17, 95% CI −0.66 to 0.31, $P = 0.483$; and overall: SMD −0.16, 95% CI −0.29 to −0.02, $P = 0.021$; Figure S5). The heterogeneity between studies was very small (overall: $I^2 = 9.2\%$, $P = 0.357$; Figure S5).

eGFR
We carried out subgroup analyses based on interventions and CKD stages (2 studies, 340 participants)[33,37]. Compared with the control group, linagliptin combined with insulin could observably improve eGFR, whereas vildagliptin combined with insulin had no obvious effect (linagliptin: SMD 0.45, 95% CI 0.14–0.76, $P = 0.005$; vildagliptin: SMD 0.07, 95% CI −0.23 to 0.37, $P = 0.654$; and overall: SMD 0.26, 95% CI −0.12 to 0.63, $P = 0.180$; Figure S6). In patients with CKD stages 3–5, the combination of DPP-4 inhibitor and insulin had no distinct effect on eGFR contrasted with the control patients (SMD 0.26,

95% CI −0.12 to 0.63, $P = 0.180$; Figure S7). There was medium heterogeneity (overall: $I^2 = 66.8\%$, $P = 0.083$; Figures S6 and S7). No obvious source of heterogeneity was found in the Galbraith plot (Figure S8). A single study test showed that a single study had little effect on the total effect (Figure S9).

FPG
Interventions were used for subgroup analysis (2 studies, 236 participants)[33,35]. Linagliptin or vildagliptin combined with insulin had no apparent influence on FPG compared with the control group (linagliptin: SMD −0.04, 95% CI −0.55 to 0.46, $P = 0.872$; vildagliptin: SMD −0.09, 95% CI −0.38 to 0.21, $P = 0.570$; Figure S10). The heterogeneity between studies was very small (overall: $I^2 = 0.0\%$, $P = 0.881$; Figure S10).

LDL-C
We accomplished a subgroup analysis based on the interventions (2 studies, 125 participants)[34,35]. Compared with the control group, linagliptin or vildagliptin combined with insulin had
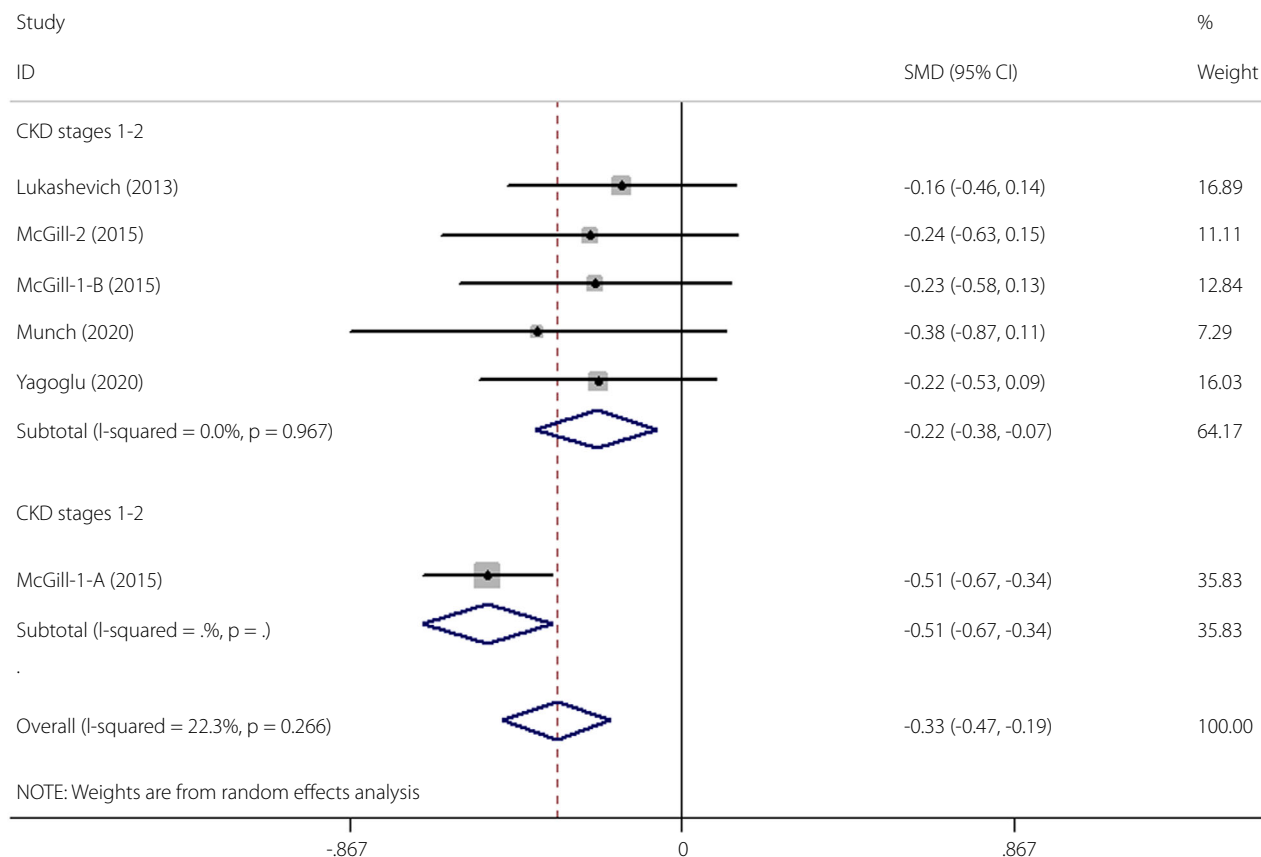
Figure 6 | Forest plot comparing glycated hemoglobin (HbA1C) of groups with chronic kidney disease (CKD) stages 1-2 or CKD stages 3-5 versus control. Left: favors combination therapy; right: favors control. CI, confidence interval; SMD, standardized mean difference.

no evident impact on LDL-C (linagliptin: SMD −0.17, 95% CI −0.68 to 0.33, $P = 0.501$; vildagliptin: SMD 0.10, 95% CI −0.38 to 0.59, $P = 0.674$; Figure S11). There was almost no heterogeneity (overall: $I^2 = 0.0\%$, $P = 0.438$; Figure S11).

UA

Subgroup analysis was carried out according to the interventions (2 studies, 224 participants)[35,37]. Linagliptin combined with insulin had no distinct influence on UA compared with the control patients (linagliptin: SMD −0.32, 95% CI −0.89 to 0.24, $P = 0.258$; Figure S12). There was high heterogeneity between studies (overall: $I^2 = 72.5\%$, $P = 0.057$; Figure S12). The Galbraith plot did not show an obvious source of heterogeneity (Figure S13). A single study test proved that a single study had no clear impact on the overall effect (Figure S14).

Weight

We used interventions for subgroup analysis (3 studies, 301 participants)[33,35,36]. Compared with the control group, linagliptin or vildagliptin combined with insulin had no noticeable impact on weight (linagliptin: SMD −0.23, 95% CI −0.74 to

0.28, $P = 0.377$; vildagliptin: SMD −0.06, 95% CI −0.31 to 0.20, $P = 0.670$; Figure S15). There was little heterogeneity among studies (overall: $I^2 = 0.0\%$, $P = 0.826$; Figure S15).

Quality of evidence

The evidence quality of all outcomes was assessed by the GRADE approach as follows: adverse event (high), eGFR (high), FPG (high), HbA1C (high), hypoglycemia (high), insulin dose (high), LDL-C (moderate), serious adverse event (high), severe hypoglycemia (high), UA (moderate) and weight (high) (Figure S16). The main defects were performance bias and detection bias (Figure S2).

Readers can find additional results of the present analysis in the supporting information.

DISCUSSION

There are a great number of patients with diabetes complicated with CKD[2]. At present, the commonly used hypoglycemic regimens are not effective in such patients, and the incidence of AEs, such as hypoglycemia, is high[11,12]. Therefore, the present study explored the effectiveness and safety of DPP-4 inhibitors bonded with insulin in this cohort, and provides a new

treatment for this kind of patient. As far as we know, no similar meta-analysis has been published to date.

The present study included linagliptin and vildagliptin. Although the two drugs have different effects on some outcomes, the overall safety and efficacy are clear.

In terms of major safety outcomes, there was not an important disparity in the rate of AEs, sAEs, hypoglycemia and severe hypoglycemia between the linagliptin or vildagliptin plus insulin group and the control group. In CKD stages 1 or 2 and CKD stages 3–5 patients, there was not a remarkable disparity in the occurrence of AEs and hypoglycemia between the DPP-4 inhibitor combined with insulin group and the control group. As a result of the low grade of heterogeneity, high grade of evidence and good consistency of results, the results support the safe use of linagliptin or vildagliptin combined with insulin in patients with CKD. In addition, rare studies have involved patients with stages 1 or 2 CKD, and more data are required to support safety in such patients.

In terms of the main efficacy outcomes, HbA1C and insulin dose decreased significantly in the linagliptin combined with insulin group, whereas there was no significant change in the vildagliptin combined with insulin group. Due to the low heterogeneity between studies, the high grade of evidence and the use of insulin in the control patients, this strongly supports the efficacy of linagliptin combined with insulin. In addition, the inclusion of CKD stages 2–5 patients in the study supports the application of linagliptin combined with insulin in CKD patients of different stages. However, there are few studies on vildagliptin combined with insulin or patients with CKD stages 1 or 2, and more data are required to support these hypotheses.

In other outcomes, linagliptin combined with insulin could observably improve eGFR contrasted with the control patients (only one study included patients with CKD stages 3–4), but there was not a prominent improvement in the vildagliptin combined with insulin group. As a result of the good grade of the evidence and the use of insulin in the control patients, this supports the amelioration of eGFR by linagliptin combined with insulin. In addition, due to the small number of studies, further studies are requisite to confirm this hypothesis.

Linagliptin or vildagliptin combined with insulin had no valid influence on FPG, LDL-C, UA or weight in patients with type 2 diabetes complicated with CKD. Due to the insufficient number of studies, the heterogeneity and evidence quality of LDL-C and UA are moderate, and the results need to be confirmed by further research.

Because of the pharmacological differences among DPP-4 inhibitors, linagliptin need not be used in patients with kidney damage, so it is commonly used in patients with type 2 diabetes and CKD[38]. The present study found that linagliptin combined with insulin decreased HbA1C and the insulin dose in patients with CKD stages 2–5 (excluding hemodialysis patients), improved eGFR in patients with CKD stages 3 or 4 (only one study was included) and had no clear impact on the rate of various AEs in patients with CKD stages 2–5. This means that linagliptin combined with insulin is suitable for CKD patients at different stages, but more evidence is required for its effect on eGFR and hemodialysis patients. As the control group was also treated with insulin, this further affirmed the efficacy of the intervention group.

A Cochrane review suggested that in patients with diabetes and CKD, DPP-4 inhibitors reduced HbA1C compared with placebo and did not affect FPG; DPP-4 inhibitors might not affect cardiovascular death, weight, heart failure, upper respiratory tract infection and liver function; the impacts of DPP-4 inhibitors on eGFR, hypoglycemia, pancreatitis, pancreatic cancer and discontinuation due to AEs were indefinite[12]. Another Cochrane review found that in diabetes patients with kidney transplantation, DPP-4 inhibitors reduced HbA1C and FPG, but not renal function contrasted with placebo; the influences of DPP-4 inhibitors on HbA1C, FPG, hypoglycemia and discontinuation due to AEs were uncertain compared with insulin glargine[39]. Some meta-analyses detected that DPP-4 inhibitors brought down HbA1C in patients with type 2 diabetes and CKD, and the rate of AEs was low[40,41]. However, none of these studies analyzed the influence of DPP-4 inhibitors combined with insulin.

The present research had the following deficiencies. First, just five studies (six trials, 1,278 participants) were included. Second, just two DPP-4 inhibitors, linagliptin and vildagliptin, were included, and there were more studies on linagliptin. Third, there were no studies on cardiovascular outcomes (cardiovascular death, myocardial infarction and stroke). Fourth, insulin was used in the control patients, which was helpful to prove the efficacy of the intervention group; however, it increased the incidence of hypoglycemia in the control group. Fifth, there was no grouping according to the type of insulin. Sixth, because only one study (Zhu et al.[35]) reported the albumin excretion rate and one study (Yagoglu et al.[37]) reported the protein-to-creatinine ratio, the pooled analysis could not be carried out.

Despite these shortcomings, the evidence quality and consistency of the main efficacy (HbA1C and insulin dose) and safety (different AEs) outcomes in the present study strongly support the application of DPP-4 inhibitors (especially linagliptin) and insulin combination therapy in patients with type 2 diabetes and CKD, providing a better option for these patients.

The research addressed the effectiveness and safety of DPP-4 inhibitors (especially linagliptin) bonded with insulin in patients with type 2 diabetes and CKD, but the protective actions of this cure on kidney and cardiovascular outcomes, as well as the effects of other DPP-4 inhibitors, need to be affirmed by more good-quality RCTs.

DISCLOSURE

The authors declare no conflict of interest.

This study complies with the Declaration of Helsinki and is not subject to ethical approval as it is a meta-analysis.

Approval of the research protocol: N/A.

Informed consent: N/A.

Approval date of registry and the registration No. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. | Study selection process.

Figure S2. | Risk of bias summary. Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias.

Figure S3. | Forest plot comparing serious adverse events (sAEs) of groups treated with linagliptin or vildagliptin combined with insulin versus control. RR, relative risk.

Figure S4. | Forest plot comparing severe hypoglycemia of groups treated with linagliptin or vildagliptin combined with insulin versus control. RR, relative risk.

Figure S5. | Forest plot comparing insulin dose of groups treated with linagliptin or vildagliptin combined with insulin versus control. SMD, standardized mean difference.

Figure S6. | Forest plot comparing estimated glomerular filtration rate (eGFR) of groups treated with linagliptin or vildagliptin combined with insulin versus control. SMD, standardized mean difference.

Figure S7. | Forest plot comparing estimated glomerular filtration rate (eGFR) of groups with chronic kidney disease (CKD) stages 1-2 or CKD stages 3–5 versus control. SMD, standardized mean difference.

Figure S8. | Galbraith plot shows the magnitude of heterogeneity between studies. se, standard error.

Figure S9. | Single study test shows the impact of a single study on the total effect. CI, confidence interval.

Figure S10. | Forest plot comparing fasting plasma glucose (FPG) of groups treated with linagliptin or vildagliptin combined with insulin versus control. SMD, standardized mean difference.

Figure S11. | Forest plot comparing low-density lipoprotein cholesterol (LDL-C) of groups treated with linagliptin or vildagliptin combined with insulin versus control. SMD, standardized mean difference.

Figure S12. | Forest plot comparing uric acid (UA) of groups treated with linagliptin or vildagliptin combined with insulin versus control. SMD, standardized mean difference.

Figure S13. | Galbraith plot shows the magnitude of heterogeneity between studies. se, standard error.

Figure S14. | Single study test shows the impact of a single study on the total effect. CI, confidence interval.

Figure S15. | Forest plot comparing the weight of groups treated with linagliptin or vildagliptin combined with insulin versus the control. SMD, standardized mean difference.

Figure S16. | Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach assesses the evidence quality of outcomes.

Table S1. | Characteristics of the included studies.

Table S2. | Outcomes of the included studies.